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ORIGINAL ARTICLE

Testing for inherited thrombophilia does not reduce the recurrence of venous thrombosis

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Summary. *Background:* Inherited thrombophilia is only weakly associated with recurrence in patients with a first venous thrombosis (VT). In spite of this, thrombophilia testing is often performed in these patients. Positive results may influence patient management such as prolonged anticoagulant treatment or intensified prophylaxis in high-risk situations. *Objective:* To investigate whether thrombophilia testing reduces the risk of recurrent VT by virtue of these management alterations. *Methods:* From a large case–control study of patients (MEGA study), aged 18–70 years, with a first VT between 1999 and 2004, we selected 197 patients who had had a recurrence during follow-up. We compared the incidence of thrombophilia testing to that of a control cohort of 324 patients. We calculated the odds ratio (OR) for recurrent thrombosis in tested vs. non-tested patients. Only patients who were tested before recurrence were regarded as tested. All first and recurrent thrombotic events were objectively confirmed. *Results:* Thrombophilia tests were performed in 35% of cases and in 30% of controls. The OR for recurrence was 1.2 [95% confidence interval (CI) 0.9–1.8] for tested vs. non-tested patients. After correction for age, sex, family history, geographic region, presence of clinical risk factors, and year of first VT, the OR remained unchanged. *Discussion:* Thrombophilia testing in patients with a first VT does not reduce the incidence of recurrence in clinical practice.

Keywords: case–control study, factor V Leiden, inherited thrombophilia, prothrombin 20210A mutation, recurrence, testing, venous thromboembolism.

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Introduction

Clinical risk factors for venous thrombosis (VT), such as recent surgery, immobilization, malignancy or pregnancy, are present in only half of all cases [1]. The discovery of various inherited thrombophilias, such as deficiencies of antithrombin, protein S and protein C, and the factor V Leiden and prothrombin 20210A mutations, has led to increased insights into the multicausal etiology of VT. These inherited thrombophilias are found in approximately 50% of patients with VT [2], and testing for thrombophilia is often performed [3]. Its use, however, is widely debated [4–7].

The presence of inherited thrombophilia is, at best, a weak predictor of recurrence in patients with a first episode of VT [8–11]. There are currently no clinical trials that compare different management strategies for patients with thrombophilia who have had a first VT. Management recommendations for patients with inherited thrombophilia, such as those in the seventh ACCP Guideline for Antithrombotic Therapy for Venous Thromboembolic Disease, are therefore graded level 2, meaning that individual patients' or physicians' values may lead to different choices [12]. This may lead to different hospital or regional guidelines on who to test for thrombophilia and on the treatment of patients who have had these tests.

Potential consequences of identifying a thrombophilic defect in a patient with a first VT include prolonging the initial anticoagulation period beyond 3–6 months, and adopting a more vigorous prophylactic regimen in high-risk situations such as surgery, immobilization, pregnancy, or the postpartum period. These strategies may reduce recurrence, but need to be balanced against hemorrhagic complications of anticoagulant treatment. In this study, we hypothesized that thrombophilia testing reduces the risk of recurrent thrombosis as a consequence of such management alterations.

Materials and methods

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study is a large population-based case–control study that includes 5051

patients, aged 18–70 years, with a first episode of VT between 1999 and 2004 [13]. In the current case–cohort study, we selected participants who were referred to either one of three anticoagulation clinics for a second episode of treatment for VT during the follow-up period until July 2007 (potential cases). We randomly sampled 385 patients who were enrolled into the MEGA study. These patients were frequency matched on the potential cases for age, sex, year of thrombotic event, and geographic region (potential controls). Only patients with proximal deep vein thrombosis and/or pulmonary embolism were included in the present analysis, as other venous thrombotic manifestations (such as upper extremity VT or superficial VT) may not carry the same risk of recurrence.

Confirmation of recurrent episodes was retrieved from the patients' treating physician and hospital records. We excluded potential cases in whom recurrence was not confirmed by objective tests. All charts were reviewed for the presence of tests for activated protein C (APC) resistance, the FV Leiden mutation or prothrombin 20210A mutation, and antithrombin, protein C and protein S levels. If any of these tests were performed within a year after the first event, we regarded patients as tested. The presence of risk factors during the first VT was assessed with structured questionnaires. Family history was regarded positive when one or more first-degree relatives had ever experienced VT.

For research purposes, DNA samples were obtained from each participant either by blood draw or buccal swab 3 months after cessation of anticoagulation or during anticoagulant therapy, in patients who continued therapy for over 1 year. A detailed description of blood collection and DNA analysis for the FV Leiden mutation and the prothrombin 20210A mutation in the MEGA study has been published previously [13]. The results were not disclosed to the participants or their treating physicians.

Multivariate logistic regression was used to calculate the odds ratio (OR) for recurrent VT in tested vs. non-tested patients. We adjusted for age (continuous variable), sex, year of thrombotic event, geographic region, family history, and presence of a clinical risk factor that provoked the first VT [surgery, immobilization or trauma, pregnancy, postpartum period until 6 weeks, and use of an oral contraceptive pill (OCP) or hormone replacement therapy (HRT)]. A sample size of 200 patients per group would suffice to detect an OR of 0.5 with a type I error of 0.05 (significance level) and a type II error of 0.20 (power 80%), assuming that approximately 30% of patients with a first episode of VT are tested for inherited thrombophilia. Additionally, the effect of thrombophilia testing was analyzed after stratification for the presence or absence of the FV Leiden mutation or the prothrombin mutation as determined in the testing for research purposes.

All participants provided written informed consent, and this study was approved by the institution's Medical Ethics Committee. All analyses were performed using SPSS statistical software (version 12.0.2, SPSS Inc., Chicago, IL, USA).

Results

In total, 277 participants from the original MEGA study were referred to one of the three selected anticoagulation clinics for a second episode of VT. The medical records of 258 of these 277 potential cases (93%) and of 361 of 385 potential controls (94%) were available for review. Twenty-seven cases and 37 controls were excluded because of a known malignancy. An additional 34 of the potential cases were excluded because the diagnosis of recurrent thrombosis could not be objectively confirmed. Thus, 197 cases and 324 controls were included in this analysis. DNA samples were available for 487 of 521 patients (93%); the overall incidence of the FV Leiden mutation was 14%, and that of the prothrombin 20210A mutation was 6%. Characteristics of these patients are given in Table 1.

Treating physicians tested for thrombophilia after the first episode of VT in 68 (35%) cases and in 97 (30%) controls. Three cases, for whom it could not be determined whether or not they were tested, were regarded as not tested. The OR for recurrence in tested vs. non-tested patients was 1.2 [95% confidence interval (CI) 0.9–1.8; Table 2]. Adjustment for age, sex and the presence of a clinical risk factor before the first thrombotic episode did not affect the OR (1.2, 95% CI 0.8–1.9). In patients with either the FV Leiden mutation or the prothrombin mutation, the OR for recurrence was 0.8 (95% CI 0.3–2.6), and it was 1.3 (0.8–2.1) in patients without these mutations (Table 2).

Table 1 Patient characteristics

	Patients with recurrence (cases)	Patients without recurrence (controls)
No. of patients	197	324
Male sex, *n* (%)	120 (61)	179 (55)
Mean age, years (SD)	50 (13)	49 (13)
Treatment duration of first VTE (%*)		
1–3 months	27	28
4–6 months	62	66
7–12 months	6	4
> 12 months	5	3
Risk factors for first VTE, *n* (%)		
Surgery/trauma/immobilization	48 (24)	100 (31)
Pregnancy	3 (2)	15 (5)
OCP/HRT	40 (20)	79 (24)
Idiopathic	106 (54)	130 (40)
Positive family history for VTE[†]	62 (32)	79 (24)
Factor V Leiden mutation, *n* (%[‡])	30 (16)[§]	36 (12)[¶]
Prothrombin 20210A mutation, *n* (%[‡])	11 (6)	17 (6)

VTE, venous thromboembolism; OCP, oral contraceptive pill; HRT, hormone replacement therapy. *Percentage of the number of patients for whom the initial treatment duration was retrievable. [†]Family history was regarded as positive when one or more first-degree family members had ever experienced VTE. [‡]Percentage of the number of patients for whom DNA samples were available. [§]Including one homozygous carrier and one compound heterozygous carrier. [¶]Including four compound heterozygous carriers.

Table 2 Incidence of thrombophilia tests in cases and controls, and odds ratios for recurrent venous thrombosis in tested vs. non-tested patients

Subgroups	% tested		Odds ratios for recurrence (tested vs. non-tested)*
	Cases	Controls	
All	35	30	1.2 (0.8–1.8)
Quartiles of age (in years)			
18.3–40.1 (n = 130)	51	39	1.9 (0.8–4.6)
40.1–50.9 (n = 130)	39	35	1.1 (0.4–2.5)
51.1–60.9 (n = 131)	26	29	0.9 (0.4–2.2)
61.0–69.8 (n = 130)	24	18	1.0 (0.4–2.9)
Sex			
Men	31	26	1.1 (0.6–2.0)
Women	41	35	1.4 (0.7–2.9)
Risk factors for first venous thrombosis			
Surgery/trauma/immobilization	23	21	1.2 (0.5–3.1)
OCP/HRT	60	32	3.4 (1.3–8.6)
Non/idiopathic	30	33	0.8 (0.5–1.6)
Family history of venous thrombosis			
Present	47	39	1.5 (0.7–3.1)
Absent	29	26	1.1 (0.7–1.9)
Thrombophilia†			
Present	33	33	0.8 (0.3–2.6)
Absent	36	29	1.3 (0.8–2.1)

OCP, oral contraceptive pill; HRT, hormone replacement therapy. *Adjusted for sex, age, year of first thrombotic event, presence of clinical risk factor that provoked the first thrombotic event, and positive family history, whenever applicable. †Either factor V Leiden mutation or prothrombin 20210A mutation.

Women were more often tested than men (35% vs. 26%), as were patients with a positive family history for VT (39% vs. 26%), younger patients (39% vs. 18% for first vs. fourth quartile of age), and patients with idiopathic or hormone-related VT (32% for OCP/HRT-provoked VT, 33% for idiopathic VT, and 21% for VT provoked by surgery, trauma or immobilization; Table 2). ORs for recurrent thrombosis in tested vs. non-tested individuals in these subgroups are given in Table 2.

Discussion

We hypothesized that patients with a first VT who are tested for inherited thrombophilia have a reduced risk of recurrence by virtue of management alterations, such as prolongation of initial anticoagulant treatment or intensified prophylaxis during high-risk situations. In this study, however, we found that tested patients do not have a different recurrence risk from non-tested patients. These results were similar in the subgroup of patients with the FV Leiden mutation or the prothrombin mutation, as determined by research testing. A possible explanation for the absence of an effect of testing may be that in clinical practice, thrombophilia tests are regularly performed, but the results are often not used for management decisions in that particular patient. This was confirmed in a recent survey among Dutch physicians who ordered tests for inherited thrombophilia [3].

Strikingly, we found that in the subgroup of women with an OCP-provoked or HRT-provoked VT, testing for thrombophilia was associated with an increased risk of recurrence. We hypothesized that an explanation, besides chance variation, could be that women who have had an OCP/HRT-provoked VT do not discontinue the use of the OCP or HRT after they are found to have no thrombophilia. However, the percentages of women who continued oral contraceptive use after their VT was the same for tested and non-tested women (18% and 17%, respectively), and for women who were tested and found not to have the FV Leiden mutation or the prothrombin mutation (18%). Therefore, we were not able to explain the cause of the increased recurrence risk in tested women with an OCP/HRT-provoked VT.

In spite of our efforts to collect data for each individual patient of this large cohort, some information was not retrievable. First, we were only able to analyze the influence of the most common inherited thrombophilias, and second, we did not assess in how many patients the test results led to management alterations. However, as the incidence of deficiencies of the natural anticoagulants is very low [14], we are confident that knowledge of other thrombophilia test results would not affect our conclusions. The second limitation is also a major strength, as the difference in observed recurrent VT between tested and non-tested patients reflects the current clinical practice of thrombophilia testing. Finally, we cannot rule out the presence of unknown patient-specific factors, associated with an increased risk of recurrent events, that lead physicians to order tests in these patients. This is not a likely explanation for the absence of a positive effect of testing, as we cannot think of any other factors, others than those that we have corrected for, that may influence the individual physician's decision to test for thrombophilia and are clearly associated with an increased risk of recurrence. Strengths include the few patients lost to follow-up (7%) and the objective confirmation of first and recurrent VT events, as well as thrombophilia tests, through source data verification. Furthermore, the patients originated from three different geographic regions in The Netherlands, and as we found no regional differences, it is likely that these results apply to the entire country.

We conclude that thrombophilia testing in patients with a first VT, as it is currently used in clinical practice, does not reduce the incidence of recurrence. Ideally, the value of testing should be investigated in a trial in which the tests have clear and uniform consequences. This was the purpose of a randomized trial (Dutch trial register, trial no. NTR784; http://www.trialregister.nl) that has recently been stopped due to slow recruitment. Nevertheless, such a trial could only test one or a few of a myriad of potential consequences of a positive test, so the judgement of the value of testing for thrombophilia will ideally be based on experimental and observational data. With the current knowledge, the value of routine testing of patients with a first VT remains questionable, and may lead to overtreatment with hemorrhagic complications or unnecessary concern in those tested positive [15,16].

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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